Summary

Whether drug-based or target-based screens are used, it is possible to exploit the detailed information gathered for several model organisms that are genetically tractable. Such approaches are well suited to identifying drugs that have a selective killing capacity for the tumor context. They allow us to escape from strategies that are based on inhibiting the activities of oncogene products, or attempting to restore the lack of activity resulting from the inactivation of a tumor suppressor gene product. Because such genetic approaches allow an alignment of particular molecular defects with "specific" drugs, there is a high probability that the serious side effects associated with many currently used chemotherapeutics will be less problematic. Although the utility of genetics and model organisms is potentially quite broad, three inadequacies will continue to limit clinical applications. The first stems from the current difficulties in understanding the complexities of the mammalian cell signaling circuitry, the second stems from our still limited methods of assessing molecular alterations in tumors, and the third stems from relatively ineffective ways of conditional gene inactivation in mammalian cells. Finally, as more therapies are developed for particular molecular defects, there will be increased need as well as incentive to improve methods for detecting these alterations.

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Environment and Cancer: Who Are Susceptible?

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Acting in concert with individual susceptibility, environmental factors such as smoking, diet, and pollutants play a role in most human cancer. However, new molecular evidence indicates that specific groups—characterized by predisposing genetic traits or ethnicity, the very young, and women—may have heightened risk from certain exposures. This is illustrated by molecular epidemiologic studies of environmental carcinogens such as polycyclic aromatic hydrocarbons and aromatic amines. Individual genetic screening for rare high-risk traits or for more common, low-penetrant susceptibility genes is problematic and not routinely recommended. However, knowledge of the full spectrum of both genetic and acquired susceptibility in the population will be instrumental in developing health and regulatory policies that increase protection of the more susceptible groups from risks of environmental carcinogens. This will necessitate revision of current risk assessment methodologies to explicitly account for individual variation in susceptibility to environmental carcinogens.

Most cancer results from the interaction of genetics and the environment (*1*–*3*). That is, genetic factors by themselves are thought to explain only about 5% of all cancer (*3*). The remainder can be attributed to external, "environmental" factors that act in conjunction with both genetic and acquired susceptibility. This is an optimistic message for cancer prevention in that exposure to environmental carcinogens—tobacco smoke, dietary constituents, pollutants (in the workplace, air, water, and food supply), drugs, radiation, and infectious agents—is theoretically preventable. But it challenges scientists to document environment-susceptibility interactions and policy-makers to rapidly

translate this knowledge into public health interventions. The pressure is great: 560,000 people die of cancer every year in the United States (6.6 million worldwide), and almost 1.4 million new cases are diagnosed in the United States annually (*4*).

The two parallel approaches in prevention are (i) strategies to help individuals modify hazardous lifestyles or use chemoprevention, and (ii) reduction of involuntary exposure to carcinogens, usually through regulation. Both approaches have been stymied by our inability to explicitly address risks to sensitive subsets of the population. Historically, policy-makers such as the U.S. Environmental Protection Agency have based their decisions on the assumption that all individuals in a population have the same biologic response to a specified dose of a carcinogen. These policymakers are only now becoming aware of the need to account for interindividual variation in susceptibility, especially as it affects risks to children (*5*, *6*).

What do we know about risks to specific populations? With respect to specific exposures? Specific cancers? How can this knowledge be applied to cancer prevention?

Here, I discuss in some detail four categories of susceptibility factors—genetic predisposition, ethnicity, age, and gender—and, more briefly, health and nutritional impairment (Fig. 1). Molecular epidemiology, a relatively new approach that uses biomarkers to study risk factors in populations, has documented striking interactions between exposure and susceptibility factors in determining cancer risk. I will draw upon molecular data from three representative types of biomarkers: polymorphisms in genes encoding metabolic/detoxification enzymes, carcinogen-DNA adducts, and mutational spectra in reporter genes. Much of the research relates to variation in susceptibility to two classic environmental carcinogens: polycyclic aromatic hydrocarbons (PAH), generated from the combustion of fossil fuels, and aromatic amines, which are present in cigarette smoke and other environmental media. Both PAH and aromatic amines are major etiologic factors in lung, bladder, and possibly breast cancers. These examples vividly illustrate the complexity of environment-susceptibility interactions.

The selected biomarkers are mechanistically relevant to cancer (*1*, *7*, *8*). Variations in the expression or form of the so-called metabolic genes, such as the P450, glutathione S-transferase (GST), and *N*-acetyltransferase (NAT) genes, strongly influence individual biologic response to carcinogens. Carcinogenic residues bound to DNA or surrogate proteins (known as adducts) provide both a fingerprint of exposure and an indicator of procarcinogenic DNA damage. In general, more PAH-DNA adducts are formed in persons who smoke or are exposed to PAH in the workplace and ambient air. However, various studies have shown considerable interindividual variation in carcinogen-DNA binding (on the order of a 30- to 50-fold difference) under equivalent conditions of exposure (*1*). PAH-DNA adducts, especially those formed by the carcinogen benzo[a]pyrene (BP) diol epoxide (BPDE), have been linked to an increased risk of lung cancer (*9*). Similarly, smokers have more hemoglobin adducts formed by the aromatic amine 4-aminobiphenyl (4-ABP); a number of studies have associated these adducts with an increased risk of bladder cancer (*10*). Finally, the *P53* tumor suppressor gene is mutated in 40 to 50% of lung, breast, colon, and other common tumors; the mutational spectrum varies by cancer type and by environmental exposure, providing clues to the specific risk factors involved (*8*). In some cases, the patterns have been consistent with both the types of DNA adducts and the mutations induced experimentally by the compound (*8*, *11*). For example, *P53* mutations in lung and breast tumors are predominantly G → T transversions, which are induced experimentally by BP and are increased in a dose-dependent manner in smokers with lung cancer (*8*, *12*). Coming full circle, it appears that the formation of both adducts and *P53* mutations in response to exposure is strongly modulated by polymorphisms in metabolic genes. Thus, these three types of biomarkers have been proposed to be early indicators of cancer risk, although there is debate over their specific application to public health policy (*1*, *7*, *13*).

Genetic Susceptibility

Genetic factors that contribute to cancer susceptibility include rare, highly penetrant, dominant mutations as well as more common genetic polymorphisms that influence individual response to environmental exposures (*1–3*, *13*, *14*). Retinoblastoma, Wilms' tumor, and a subset of breast and ovarian cancers (Li-Fraumeni syndrome) are examples of cancers affected by rare, dominant mutations. Other "high-risk" genetic disorders are xeroderma pigmentosum (XP) and ataxia telangiectasia (AT). These traits can confer very high lifetime cancer risks to the affected individuals, but they explain only a small fraction of cancer incidence.

Although they pose low individual risk, more common genetic traits—such as those that influence the metabolic activation or detoxification of carcinogenic chemicals—

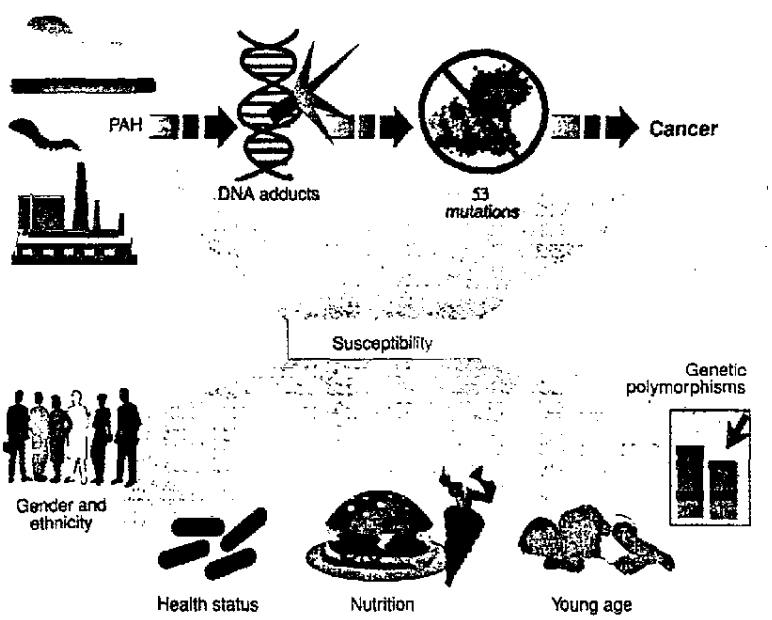

Fig. 1. A proposed pathway for environmental carcinogenesis, which begins when exposure to PAH, formed from incomplete combustion processes, leads to the formation of PAH-DNA adducts. These adducts can cause mutations in critical genes such as *P53*. The mutations alter the normal functions of the proteins; in this case, the DNA-binding domain of *P53* (blue) loses the ability to complex with DNA (yellow). A succession of mutations in other critical genes leads to cancer. The entire pathway is thought to be influenced by susceptibility factors such as gender and ethnicity, health status, nutrition, young age, and genetic polymorphisms. Molecular epidemiologic approaches are currently being used to investigate this proposed pathway and the role of these suspected susceptibility factors.

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